430 Rec'd PCT/PTO 22 FEB 2000

FORM PTO-1390 (REV 10-95) | U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY'S DOCKET NUMBER: MERCK 2075 PCT

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U S APPLICATION NO. (If known, see 37 CFR §1 5): 09/486062

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/05161	14 August 1998	23 August 1997

TITLE OF INVENTION: CYCLOPEPTIDE DERIVATIVES

APPLICANT(S) FOR DO/EO/US: Günter HÖLZEMANN, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau)
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3))
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 13. to 19. below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R §§3 28 and 3.31 is included.
15. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

    Letter
    PCT/IB/304
    PCT/IB/308

U.S. APPLICATION NO (if known, see 37 CFR §1 5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/486062	PCT/EP98/05161	MERCK 2075

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):		
Search Report has been prepared by the EPO or JPO. $840.00		
International preliminary examination fee paid to USPTO (37 CFR §1.482) $670.00		
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1 445(a)(2)) $760.00		
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... .... $970.00		
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... ..... $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ■ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).	$130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	10 - 20 =	0	x $ 18.00	$0.00	
Independent claims	1 - 3 =	0	x $ 78.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 260.00		
TOTAL OF ABOVE CALCULATIONS =				$970.00	
Reduction of ½ for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C F.R. §§1.9, 1.27, 1.28).					
SUBTOTAL =				$970.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$970.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$970.00	
				Amount to be refunded:	
				charged:	

a. ☒ A check in the amount of $970.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

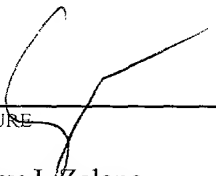
NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 243-6333

Filed: 02/22/00

AJZ:jvbp



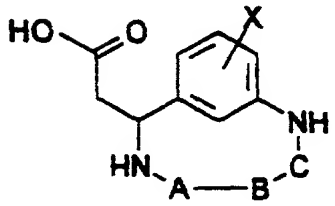
SIGNATURE

Anthony J. Zelano
NAME

27,969
REGISTRATION NUMBER

Cyclopeptide derivatives

The invention relates to compounds of the formula I



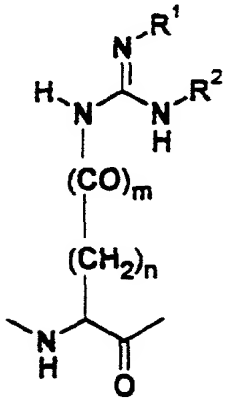
I

,

in which

A is Gly, Ala or NH-NH-CO, where the amino acids mentioned can also be derivatized,

B is a radical of the formula II



II

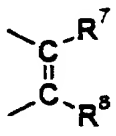
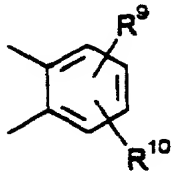
,

C is $-(CO)_p-(CH_2)_q-(CO)_r-$ or $-(CO)_p-CH=CH-(CO)_r-$,

m, p, r in each case independently of one another are 0 or 1,

n, q in each case independently of one another are 1, 2, 3 or 4,

R^1 and R^2 in each case independently of one another are H or alkyl,

R^1 and R^2 together are also R^7, R^8, R^9,  or 

R^{10} in each case independently of one another are H, alkyl, Ar, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,

X is H, Hal, alkyl or Ar,

Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by R^3, R^4 or R^5 or is unsubstituted naphthyl,

R^3, R^4, R^5 in each case independently of one another are R^6, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,

R^6, $R^{6'}$ in each case independently of one another are H, alkyl, phenyl or benzyl, and

Hal is F, Cl, Br or I,

and if there are radicals of optically active amino acids and amino acid derivatives, both the D and the L forms are included,

and their salts.

Similar compounds of cyclic peptides are disclosed, for example, in DE 43 10 643 or EP 0 683 173.

The invention is based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties combined with good tolerability. They act especially as integrin inhibitors, in particular inhibiting the interactions of the α_v-, β_3- or β_5-integrin receptors with ligands, such as, for example, the binding of fibrinogen to the β_3-integrin receptor. The compounds show particular activity in the case of the integrins $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_6$ and $\alpha_v\beta_8$.

This action can be demonstrated, for example, by the method which is described by J.W. Smith et al. in J. Biol. Chem. 265, 12267-12271 (1990).

The dependence of the origin of angiogenesis on the interaction between vascular integrins and extracellular matrix proteins is described by

P.C. Brooks, R.A. Clark and D.A. Cheresh in Science 264, 569-71 (1994).

The possibility of the inhibition of this interaction and thus for the initiation of apoptosis (programmed cell death) of angiogenic vascular cells by a cyclic peptide is described by P.C. Brooks, A.M. Montgomery, M. Rosenfeld, R.A. Reisfeld, T.-Hu, G. Klier and D.A. Cheresh in Cell 79, 1157-64 (1994).

Compounds of the formula I which block the interaction of integrin receptors and ligands, such as, for example, of fibrinogen on the fibrinogen receptor (glycoprotein IIb/IIIa), prevent, as GPIIb/IIIa antagonists, the spread of tumour cells by metastasis. This is confirmed by the following observations:

The spread of tumour cells from a local tumour into the vascular system takes place through the formation of microaggregates (microthrombi) by interaction of the tumour cells with blood platelets. The tumour cells are screened by protection in the microaggregate and are not recognized by the cells of the immune system.

The microaggregates can fix to vascular walls, by means of which a further penetration of tumour cells into the tissue is facilitated.

Since the formation of the microthrombi is mediated by fibrinogen binding to the fibrinogen receptors on activated blood platelets, the GPIIa/IIIb antagonists can be regarded as effective metastasis inhibitors.

The compounds of the formula I can be employed as pharmaceutical active compounds in human and veterinary medicine, in particular for the prophylaxis and/or therapy of diseases of the circulation, thrombosis, myocardial infarct, arteriosclerosis, inflammations, apoplexy, angina pectoris, oncoses, osteolytic diseases such as osteoporosis, pathologically angiogenic diseases such as, for example, inflammations, ophthalmological diseases, diabetic retinopathy, macular degeneration, myopia, ocular histoplasmosis, rheumatoid arthritis, osteo-

arthritis, rubeotic glaucoma, ulcerative colitis, Crohn's disease, atherosclerosis, psoriasis, angiogenesis and restenosis after angioplasty, viral infection, bacterial infection, fungal infection, in acute kidney failure and in wound healing for supporting the healing processes.

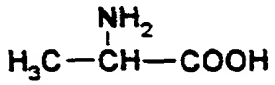
The compounds of the formula I can be employed as substances having antimicrobial activity in operations where biomaterials, implants, catheters or heart pacemakers are used.
They have an antiseptic action here. The efficacy of the antimicrobial activity can be demonstrated by the procedure described by P. Valentin-Weigund et al., in Infection and Immunity, 2851-2855 (1988).

Since the compounds of the formula I are inhibitors of fibrinogen binding and thus ligands of the fibrinogen receptors on blood platelets, they can be used *in vivo* as diagnostics for the detection and localization of thrombi in the vascular system, provided they are substituted, for example, by a radioactive or UV-detectable residue.

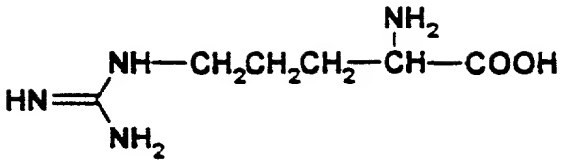
The compounds of the formula I can be used as inhibitors of fibrinogen binding and as effective auxiliaries for the study of the metabolism of blood platelets in different activation stages or of intracellular signal mechanisms of the fibrinogen receptor. The detectable unit of a "label" to be incorporated, e.g. isotopic labelling by ^3H, allows, after binding to the receptor, the mechanisms mentioned to be investigated.

The abbreviations of amino acid residues listed above and below stand for the radicals of the following amino acids:

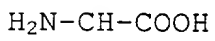
Ala alanine



Arg arginine



Gly glycine



Furthermore, the following have the meanings below:

Ac	acetyl
Boc	tert-butoxycarbonyl
CBZ or Z	benzyloxycarbonyl
DCCI	dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EDCI	N-ethyl-N,N'-(dimethylaminopropyl)carbodiimide
Et	ethyl
FCA	fluoresceincarboxylic acid
Fmoc	9-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
HONSu	N-hydroxysuccinimide
MBHA	4-methylbenzhydrylamine
Me	methyl
Mtr	4-methoxy-2,3,6-trimethylphenylsulfonyl
NMM	N-methylmorpholine
OBzl	benzyl ester
Oct	octanoyl
OEt	ethyl ester
OMe	methyl ester
OtBu	tert-butyl ester
POA	phenoxyacetyl
Sal	salicyloyl
TFA	trifluoroacetic acid
Trt	trityl (triphenylmethyl).

If the abovementioned amino acids can occur in several enantiomeric forms, then above and below, e.g. as a constituent of the compounds of the formula I, all these forms and also their mixtures (e.g. the DL forms) are included. Furthermore, the amino acids can be provided, e.g. as a constituent of compounds of the formula I, with corresponding protective groups which are known per se.

So-called prodrug derivatives are also included in the compounds according to the invention, i.e. compounds of the formula I, modified with, for example, alkyl or acyl groups, sugars or oligopeptides, which are rapidly cleaved in the body to the active compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as is described, for example, in Int. J. Pharm. 115, 61-67 (1995).

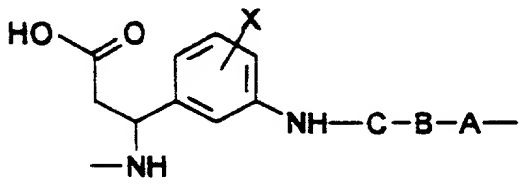
Amino acids whose configuration is not specifically indicated have the (S) or (L) configuration.

The invention further relates to a process for the preparation of compounds of the formula I according to Claim 1 and of their salts, characterized in that

(a) a compound of the formula III

H-Z-OH III

in which

Z is 

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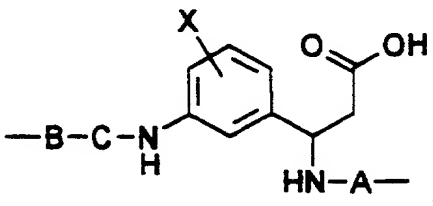

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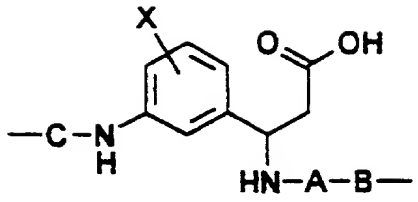
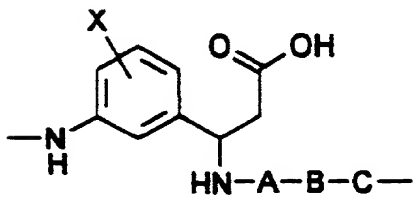


or



and X, A, B, and C have the meanings indicated in Claim 1,

or a reactive derivative of a compound of the formula III is treated with a cyclizing agent,

or

b) a compound of the formula I is set free from one of its functional derivatives by treating with a solvolysing or hydrogenolysing agent,

and/or in that a basic or acidic compound of the formula I is converted into one of its salts by treating with an acid or base.

Above and below, the radicals X, A, B, C, R^1, R^2, m, n, p, q and Z have the meanings indicated in the formulae I, II and III, if not expressly stated otherwise.

In the above formulae, X is preferably H, Hal or alkyl, in particular H, Cl or CH_3.

In the above formulae, alkyl has 1-6 C atoms and is preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, and further also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl. Alkyl is particularly preferably methyl.

R^7, R^8, R^9 and R^{10} are preferably H.

The amino acids and amino acid residues mentioned can also be derivatized, the N-methyl, N-ethyl, N-propyl, N-benzyl or C_α-methyl derivatives being preferred.

Additionally preferred, in particular, are the methyl, ethyl, propyl, butyl, tert-butyl, neopentyl or benzyl esters of the side chain carboxyl group, and further also derivatives of arginine, which can be substituted on the $-NH-C(=NH)-NH_2$ group by an acetyl, benzoyl, methoxycarbonyl or ethoxycarbonyl radical.

R^6 and $R^{6'}$ are preferably, for example, H, methyl or ethyl, and further benzyl or phenyl.

OR^6 is preferably, for example, hydroxyl or methoxy.

COR^6 is alkanoyl and is preferably formyl, acetyl, propionyl, butyryl, pentanoyl or hexanoyl.

Ar is phenyl which is unsubstituted, preferably - as indicated - monosubstituted, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-(trifluoromethoxy)-phenyl, o-, m- or p-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-benzyloxycarbonylphenyl, o-, m- or p-(carboxymethyloxy)phenyl, o-, m- or p-(methoxycarbonylmethyloxy)phenyl, o-, m- or p-(methoxycarbonyl-ethyloxy)phenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N-ethylamino)-phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-difluoromethoxy)phenyl, o-, m- or p-(fluoromethoxy)phenyl, o-, m- or p-formylphenyl, o-, m- or p-acetylphenyl, o-, m- or p-propionylphenyl, o-, m- or p-butyrylphenyl, o-, m- or

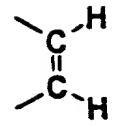
p-pentanoylphenyl, o-, m- or p-(methylsulfonamido)-phenyl, o-, m- or p-phenoxyphenyl, o-, m- or p-methylthiophenyl, o-, m- or p-methylsulfinylphenyl, o-, m- or p-methylsulfonylphenyl or naphthyl.

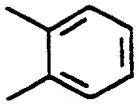
Amino protective group preferably denotes acetyl, propionyl, butyryl, phenylacetyl, benzoyl, toluyl, POA, methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, Boc, 2-iodoethoxy-carbonyl, CBZ ("carbobenzoxy"), 4-methoxybenzyloxy-carbonyl, Fmoc, Mtr or benzyl.

The compounds of the formula I have at least two chiral centres and can therefore occur in various stereoisomeric forms. The formula I includes all these forms.

Accordingly, the invention relates in particular to those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following subformulae Ia, Ib and Ic, which correspond to the formula I and in which

in Ia	X	is H, alkyl or Hal,
	R^1, R^2	are H,
	m	is 0,
	n	is 3,
	p, r	are 1, and
	q	is 2 or 3, and
in Ib	X	is H, alkyl or Hal,
	R^1, R^2	are H,
	m	is 0,
	n	is 3,
	p	is 1,
	r	is 0, and
	q	is 1, and
in Ic	X	is H, alkyl or Hal,

R^1 and R^2 together are  or



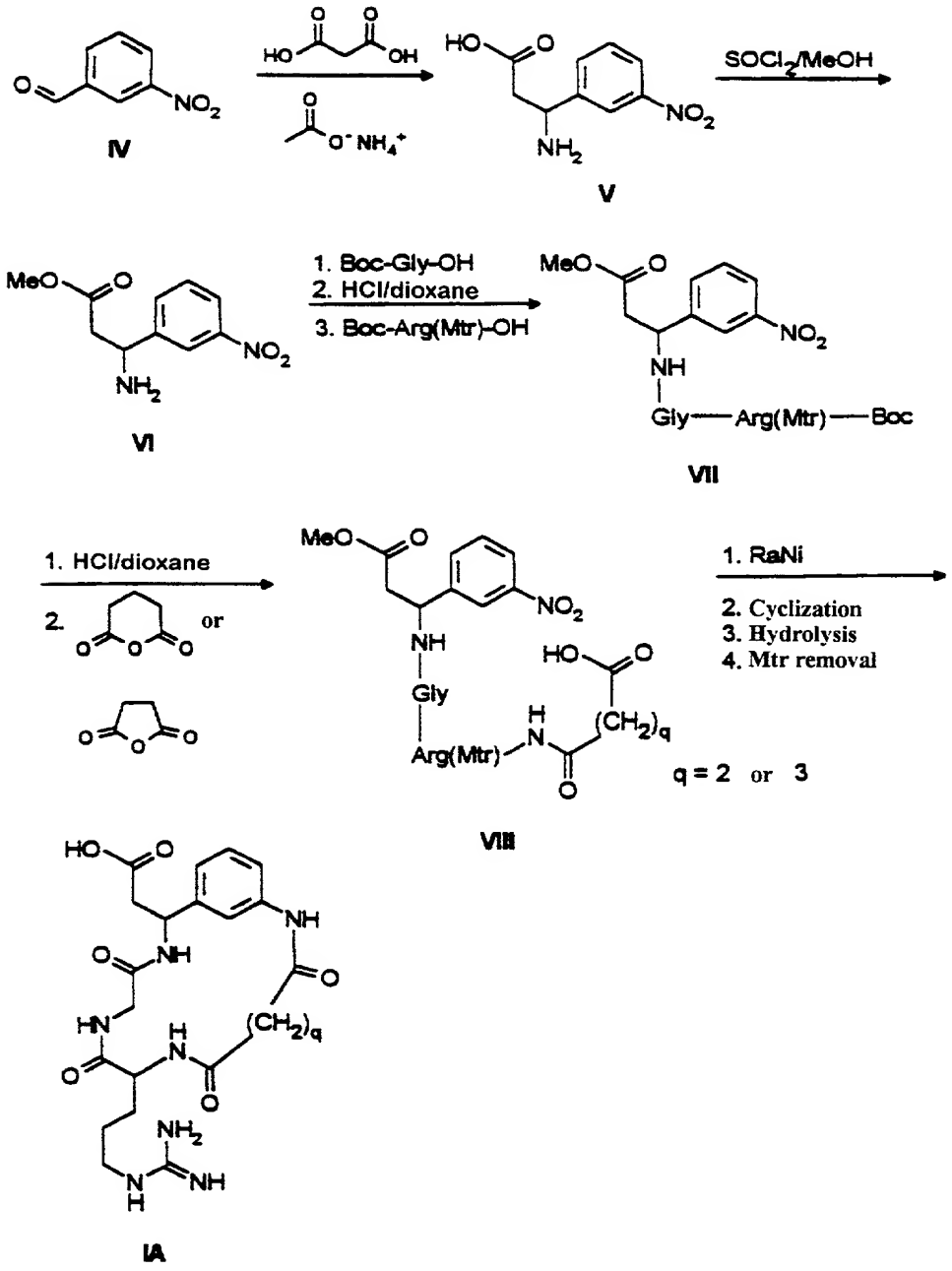
m	is 1
n	is 2
p, r	are 1, and
q	is 2.

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. In this case, use can also be made of variants which are known per se but not mentioned here in greater detail.

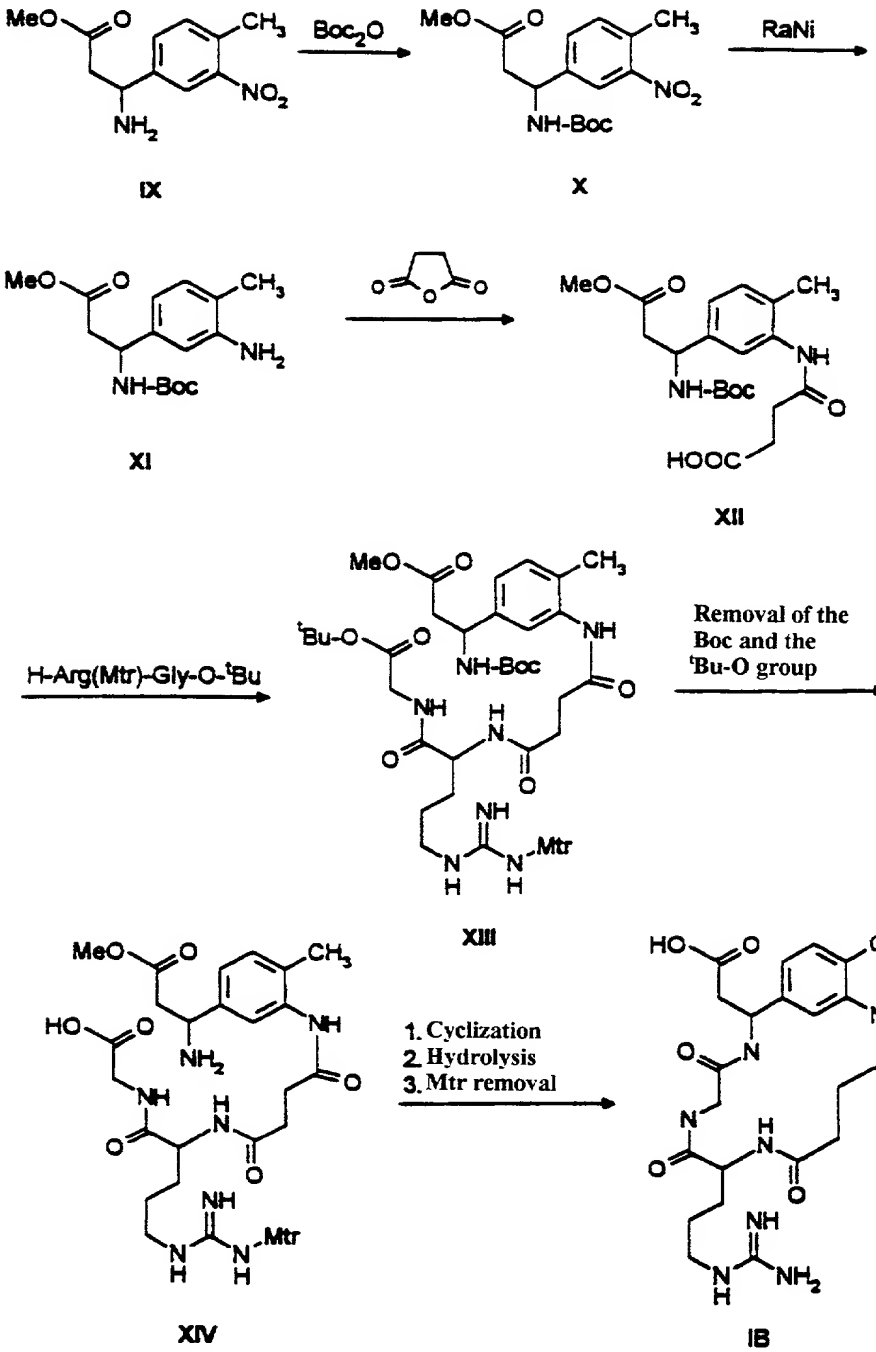
If desired, the starting substances can also be formed in situ such that they are not isolated from the reaction mixture, but are immediately reacted further to give the compounds of the formula I.

The compounds of the formula I can be prepared, for example, according to the following schemes 1 and 2:

Scheme 1:


IV
V
VI
VII
VIII
IA
SOCl2/MeOH
1. Boc-Gly-OH
2. HCl/dioxane
3. Boc-Arg(Mtr)-OH
1. HCl/dioxane
2.
or
1. RaNi
2. Cyclization
3. Hydrolysis
4. Mtr removal
q = 2 or 3

Scheme 2:


MeO
O
CH3
NO2
NH2
Boc2O
NH-Boc
RaNi
IX
X
NH
HOOC
XI
XII
H-Arg(Mtr)-Gly-O-tBu
tBu-O
Mtr
XIII
Removal of the
Boc and the
tBu-O group
HO
1. Cyclization
2. Hydrolysis
3. Mtr removal
XIV
IB

The important 3-amino-3-(3-nitrophenyl)-propionic acid unit from Scheme 1 is prepared according to J. Org. Chem. 25, 1758 (1960) from 3-nitrobenzaldehyde, malonic acid and ammonium acetate. In the synthesis of analogous compounds the corresponding nitrobenzaldehyde derivatives are used.

Compounds of the formula I can preferably be obtained by cyclization of compounds of the formula III under the conditions of a peptide synthesis. In this case, the reaction is expediently carried out by customary methods of peptide synthesis, such as are described, for example, in Houben-Weyl, l.c., Volume 15/II, pages 1 to 806 (1974).

The reaction preferably takes place in the presence of a dehydrating agent, e.g. of a carbodiimide such as DCCI or EDCI, and further, for example, propanephosphonic anhydride (cf. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxy-carbonyl-1,2-dihydroquinoline, in an inert solvent, e.g. a halogenated hydrocarbon such as dichloromethane, an ether such as tetrahydrofuran or dioxane, an amide such as DMF or dimethylacetamide, a nitrile such as acetonitrile, in dimethyl sulfoxide or in the presence of these solvents, at temperatures between approximately -10 and 40, preferably between 0 and 30°. In order to promote intramolecular cyclization ahead of intermolecular peptide bonding, it is expedient to work in dilute solutions.

Depending on the conditions used, the reaction time is between a few minutes and 14 days.

Instead of compounds of the formula III, it is also possible to employ derivatives of compounds of the formula III, preferably a preactivated carboxylic acid, or a carboxylic acid halide, a symmetrical or mixed anhydride or an active ester. Radicals of this type for the activation of the carboxyl group in typical acylation reactions are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic

Chemistry], Georg-Thieme-Verlag, Stuttgart). Activated esters are expediently formed in situ, e.g. by addition of HOBt or N-hydroxysuccinimide.

As a rule, the reaction is carried out in an inert solvent, when using a carboxylic acid halide in the presence of an acid-binding agent, preferably of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline.

The addition of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or of another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium, calcium or caesium, may also be favourable.

As a rule, the starting substances of the formula III are novel. They can be prepared by known methods of peptide synthesis.

The compounds of the formula I can further be obtained by setting them free from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

Preferred starting substances for the solvolysis or hydrogenolysis are those which, instead of one or more free amino and/or hydroxyl groups, contain corresponding protected amino and/or hydroxyl groups, preferably those which, instead of an H atom which is bonded to an N atom, carry an amino protective group, e.g. those which correspond to the formula I but instead of an NH_2 group contain an NHR' group (in which R' is an amino protective group, e.g. Boc or CBZ).

Starting substances are furthermore preferred which, instead of the H atom of a hydroxyl group, carry a hydroxyl protective group, e.g. those which correspond to the formula I but instead of a hydroxyphenyl group contain an R"O-phenyl group (in which R" is a hydroxyl protective group).

A plurality of - identical or different - protected amino and/or hydroxyl groups can also be present in the molecule of the starting substance. If the

protective groups present are different from one another, in many cases they can be selectively removed.

The expression "amino protective group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise not critical; however, those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" is to be interpreted in the widest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and also, in particular, alkoxycarbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or toluyl; aryloxyalkanoyl such as POA; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, Boc, 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl, Fmoc; arylsulfonyl such as Mtr. Preferred amino protective groups are Boc and Mtr, and further CBZ, Fmoc, benzyl and acetyl.

The expression "hydroxyl protective group" is likewise generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule. Typical of such groups are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, and fur-

thermore also alkyl groups. The nature and size of the hydroxyl protective groups is not critical, since they are removed again after the desired chemical reaction or reaction sequence; groups having 1-20, in particular 1-10, C atoms are preferred. Examples of hydroxyl protective groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, benzyl and tert-butyl being particularly preferred. The COOH group is preferably protected in the form of its tert-butyl ester.

The compounds of the formula I are set free from their functional derivatives - depending on the protective group used - e.g. using strong acids, expediently using TFA or perchloric acid, but also using other strong inorganic acids such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids such as trichloroacetic acid or sulfonic acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic solvents, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran or dioxane, amides such as DMF, halogenated hydrocarbons such as dichloromethane, and further also alcohols such as methanol, ethanol or isopropanol, and also water. Mixtures of the abovementioned solvents are furthermore suitable. TFA is preferably used in an excess without addition of a further solvent, perchloric acid in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are expediently between approximately 0 and approximately 50°, preferably the cleavage is carried out between 15 and 30° (room temperature).

The groups Boc, OtBu and Mtr can, for example, preferably be removed using TFA in dichloromethane or using approximately 3 to 5 N HCl in dioxane at 15-30°, the Fmoc group using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

The trityl group is employed for the protection of the amino acids histidine, asparagine, glutamine and cysteine. Removal is carried out, depending on the desired final product, using TFA/10% thiophenol, the trityl group of all amino acids mentioned being removed, when using TFA/anisole or TFA/thioanisole only the trityl group of histidine, asparagine and glutamine being removed, while it remains on the cysteine side chain.

Hydrogenolytically removable protective groups (e.g. CBZ or benzyl) can be removed, for example, by treating with hydrogen in the presence of a catalyst (e.g. of a noble metal catalyst such as palladium, expediently on a support such as carbon). Suitable solvents here are those indicated above, in particular, for example, alcohols such as methanol or ethanol or amides such as DMF. As a rule, the hydrogenolysis is carried out at temperatures between approximately 0 and 100° and pressures between approximately 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group is readily carried out, for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

A base of the formula I can be converted into the associated acid addition salt using an acid, for example by reaction of equivalent amounts of the base and of the acid in an inert solvent such as ethanol and subsequent evaporation. In particular, acids which yield physiologically acceptable salts are suitable for this reaction. Thus inorganic acids can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, and furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid,

pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and disulfonic acids, laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, an acid of the formula I can be converted into one of its physiologically acceptable metal or ammonium salts by reaction with a base. Possible salts in this case are, in particular, the sodium, potassium, magnesium, calcium and ammonium salts, and furthermore substituted ammonium salts, e.g. the dimethyl-, diethyl- or diisopropylammonium salts, monoethanol-, diethanol- or diisopropylammonium salts, cyclohexyl- or dicyclohexylammonium salts, dibenzyl-ethylenediammonium salts, and furthermore, for example, salts with arginine or lysine.

The invention further relates to the use of the compounds of the formula I and/or their physiologically acceptable salts for the production of pharmaceutical preparations, in particular in a non-chemical way. In this context, they can be brought into a suitable dose form together with at least one solid, liquid and/or semi-liquid excipient or auxiliary and, if appropriate, in combination with one or more other active compounds.

The invention furthermore relates to pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts.

These preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration, topical application or administration in the form of an inhalation spray and do not react with the novel

compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glyceryl triacetate, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc, petroleum jelly. In particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, and furthermore suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavourings and/or one or more other active compounds, e.g. one or more vitamins.

For administration as an inhalation spray, sprays can be used which contain the active compound either dissolved or suspended in a propellant or propellant mixture (e.g. CO_2 or chlorofluorohydrocarbons). Expediently, the active compound is in this case used in micronized form, it being possible for one or more additional physiologically tolerable solvents, e.g. ethanol, to be present. Inhalation solutions can be administered with the aid of customary inhalers.

The compounds of the formula I and their physiologically acceptable salts can be used as integrin inhibitors in the control of illnesses, in particular of diseases of the circulation, thromboses, cardiac infarct, coronary heart diseases, arteriosclerosis, apoplexy, angina pectoris, tumours, osteoporosis, inflammations, infections and restenosis after angioplasty.

The compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts

are also used in pathological processes which are supported or propagated by angiogenesis, in particular in tumours or rheumatoid arthritis.

In this case, the substances according to the invention can as a rule be administered in analogy to other known, commercially available peptides, but in particular in analogy to the compounds described in US-A-4 472 305, preferably in doses between approximately 0.05 and 500 mg, in particular between 0.5 and 100 mg per dose unit. The daily dose is preferably between approximately 0.01 and 2 mg/kg of body weight. The specific dose for each patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Parenteral administration is preferred.

The compounds of the formula I can furthermore be used as integrin ligands for the preparation of columns for affinity chromatography for the preparation of integrins in pure form.

The ligand, i.e. a compound of the formula I, is in this case covalently coupled to a polymeric support via an anchor function, e.g. the free carboxyl group.

Suitable polymeric supports are the polymeric solid phases, preferably having hydrophilic properties, known per se in peptide chemistry, for example crosslinked polysugars such as cellulose, Sepharose or Sephadex®, acrylamides, polymer based on polyethylene glycol or Tentakel polymers®.

The materials for affinity chromatography for integrin purification are prepared under conditions such as are customary and known per se for the condensation of amino acids.

The compounds of the formula I contain at least two chiral centres and can therefore be present in racemic or in optically active form. Racemates obtained

can be separated into the enantiomers mechanically or chemically by methods known per se. Preferably, diastereomers are formed from the racemic mixture by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Also advantageous is an enantiomer resolution with the aid of a column packed with an optically active resolving agent (e.g. dinitrobenzoylphenylglycine); a suitable eluent is, for example, a mixture of hexane/isopropanol/acetonitrile, e.g. in the volume ratio 82:15:3.

Of course, it is also possible to obtain optically active compounds of the formula I by the methods described above by using starting substances which are already optically active.

All temperatures above and below are indicated in °C. Room temperature is 22°C. In the following examples, "customary working up" means: if necessary, water is added, the mixture is adjusted, if necessary, to a pH of between 2 and 10, depending on the constitution of the final product, and extracted with ether or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallization.

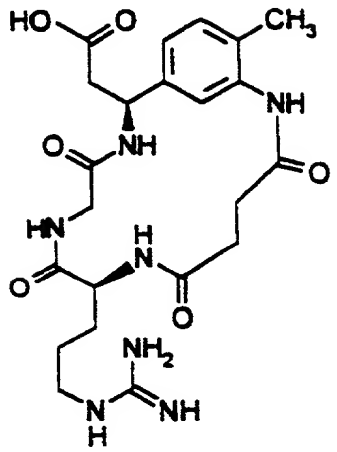
RT = retention time (minutes) on HPLC in the following systems:

Column: Lichrosorb® RP 18 (250 × 4; 5 µm)
Eluent A: 0.1% TFA in water
Eluent B: 0.1% TFA in 90% acetonitrile, 10% water
Flow rate: 1 ml/min
Gradient: 20 - 95% B/50 min
Detection at 215 nm.

The separation of the diastereomers is preferably carried out under the conditions indicated.

Mass spectrometry (MS): FAB (Fast Atom Bombardment) $(M+H)^+$

Example 1



8S, 14S-**IB**

Synthesis of the compound to be cyclized

Methyl (3R,S)-3-amino-3-(4-methyl-3-nitrophenyl)propionate (3R,S-**IX**) is synthesized analogously to Scheme 1. This ester is cleaved into the enantiomers according to the known method and methyl (3S)-3-amino-3-(4-methyl-3-nitrophenyl)propionate (3S-**IX**) is then reacted analogously to Scheme 2 to give the Mtr-protected compound methyl 3S-amino-3-(3-{3-[1-(carboxymethylcarbamoyl)-4-guanidino-1S-butylcarbamoyl]propionylamino}-4-methylphenyl)propionate (S,S-**XIV**).

Cyclization

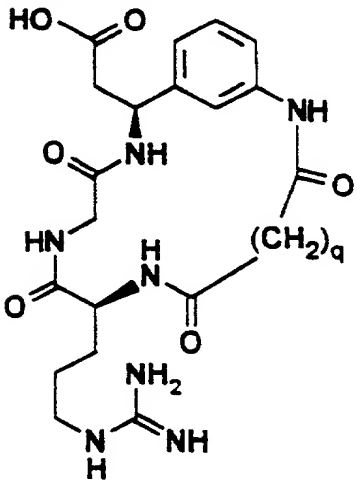
616 mg of the Mtr-protected compound methyl 3S-amino-3-(3-{3-[1-(carboxymethylcarbamoyl)-4-guanidino-1S-butylcarbamoyl]propionylamino}-4-methylphenyl)-propionate (S,S-**XIV**) are dissolved in 80 ml of DMF and diluted with 800 ml of dichloromethane. The mixture is then cooled to -20°C and 300 mg of EDCI, 98 mg of DMAP and 0.176 ml of NMM are added successively. It is warmed to room temperature and

stirred overnight. The solution is concentrated and the residue is stirred into 200 ml of half-saturated $NaHCO_3$ solution. The precipitate is filtered off with suction and washed. 400 mg of substance are obtained, which are purified by preparative HPLC. After chromatography, 44 mg of the Mtr-protected cyclic compound methyl (8S,14S)-[8-(3-guanidinopropyl)-18-methyl-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-14-yl]acetate, RT 26.1; FAB 716.

Hydrolysis and removal of the Mtr protective group

The Mtr-protected cyclic compound (8S,14S)-[8-(3-(guanidinopropyl)-18-methyl-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-14-yl] acetic acid is obtained by hydrolysis in KOH/methanol. 25 mg of this compound are then dissolved in 4.3 ml of 98% strength trifluoroacetic acid and stirred overnight at room temperature. The solution is concentrated in a rotary evaporator and the residue is purified by preparative HPLC. 9.5 mg of (8S,14S)-[8-(3-guanidinopropyl)-18-methyl-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo-[13.3.1]nonadeca-1(18),15(19),16-trien-14-yl] acetic acid (8S,14S-**IB**) are obtained, RT 20.2; FAB 490.

Examples 2-3:



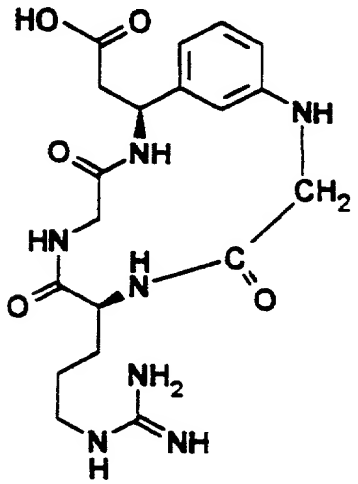
Example 2 (q = 2):

Starting from 85 mg of the Mtr-protected compound (8S,14S)-2-(8-(3-guanidinopropyl)-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]nonadeca-16,18,19-trien-14-yl) acetic acid, there are obtained, in analogy to Example 1 by reaction with 14.7 ml of 98% trifluoroacetic acid, 13 mg of (8S,14S)-2-(8-(3-guanidinopropyl)-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]nonadeca-16,18,19-trien-14-yl) acetic acid; RT 17.2; FAB 476.

Example 3 (q = 3):

Starting from 300 mg of the Mtr-protected compound (9S,15S)-2-(9-(3-guanidinopropyl)-3,7,10,13-tetraoxo-2,8,11,14-tetraazabicyclo[14.3.1]eicosan-17,19,20-trien-15-yl) acetic acid, there are obtained in analogy to Example 1, 74 mg of (9S,15S)-2-(9-(3-guanidinopropyl)-3,7,10,13-tetraoxo-2,8,11,14-tetraazabicyclo[14.3.1]eicosan-17,19,20-trien-15-yl) acetic acid; RT 18.3; FAB 490.

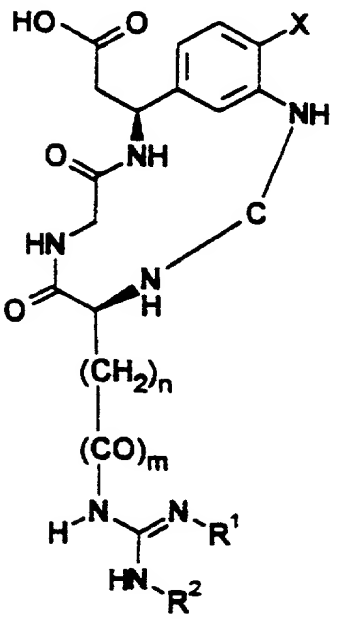
Example 4:



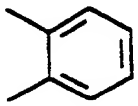
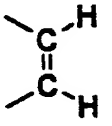
Starting from the Mtr-protected compound (6S,12S)-[6-(3-guanidinopropyl-4,7,10-trioxo-2,5,8,11-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-12-yl] acetic acid, there are obtained in analogy to

Example 1, (6S,12S)-[6-(3-guanidinopropyl-4,7,10-trioxo-2,5,8,11-tetraazabicyclo-[11.3.1]heptadeca-1(17),13,15-trien-12-yl] acetic acid.

Examples 5-8:



The following compounds are synthesized in analogy to Example 1:

Ex. No.	X	C	m	n	R^1 and R^2
5	H	-CO-CH=CH-CO-	0	3	H
6	Cl	-CO-CH_2-CH_2-CO-	0	3	H
7	CH_3	-CO-CH_2-CH_2-CO-	1	2	
8	H	-CO-CH_2-CH_2-CO-	1	2	

The following examples relate to pharmaceutical preparations:

Example A: injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is

adjusted to pH 6.5 using 2 N hydrochloric acid in 3 l of double-distilled water, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: solution

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: ointment

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

Example F: coated tablets

Analogously to Example E, tablets are pressed which are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

Example G: capsules

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: ampoules

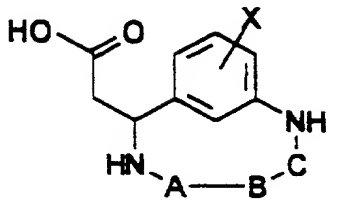
A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

Example I: inhalation spray

14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is dispensed into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One burst of spray (approximately 0.1 ml) corresponds to a dose of approximately 0.14 mg.

Patent Claims

1. Compounds of the formula I



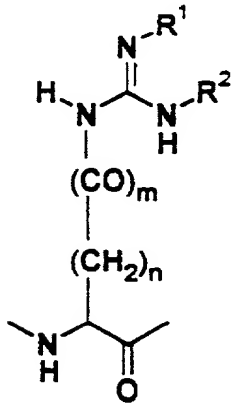
I

,

in which

A is Gly, Ala or NH-NH-CO,
where the amino acids mentioned can also be derivatized,

B is a radical of the formula II



II

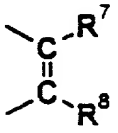
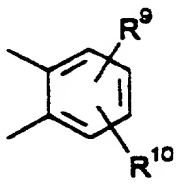
,

C is $-(CO)_p-(CH_2)_q-(CO)_r-$ or $-(CO)_p-CH=CH-(CO)_r-$,

m, p, r in each case independently of one another are 0 or 1,

n, q in each case independently of one another are 1, 2, 3 or 4,

R^1 and R^2 in each case independently of one another are H or alkyl,

R^1 and R^2 together are also  or 

R^7, R^8, R^9,

R^{10} in each case independently of one another are H, alkyl, Ar, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,

X is H, Hal, alkyl or Ar,

Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by R^3, R^4 or R^5 or is unsubstituted naphthyl,

R^3, R^4, R^5 in each case independently of one another are R^6, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,

R^6, $R^{6'}$ in each case independently of one another are H, alkyl, phenyl or benzyl, and

Hal is F, Cl, Br or I,

and if there are radicals of optically active amino acids and amino acid derivatives, both the D and the L forms are included,

and their salts.

2. An enantiomer or a diastereomer of a compound of the formula according to Claim 1.

3. Compounds of the formula I according to Claim 1:

a) (8S,14S)-2-(8-(3-guanidinopropyl)-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]nonadeca-16,18,19-trien-14-yl)acetic acid;

b) (9S,15S)-2-(9-(3-guanidinopropyl)-3,7,10,13-tetraoxo-2,8,11,14-tetraazabicyclo[14.3.1]eicosan-17,19,20-trien-15-yl)acetic acid;

c) (8S,14S)-(8-(3-guanidinopropyl)-18-methyl-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]-nonadeca-1(18),15(19),16-trien-14-yl)acetic acid;

d) (6S,12S)-(6-(3-guanidinopropyl)-4,7,10-trioxo-2,5,8,11-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-12-yl)acetic acid;

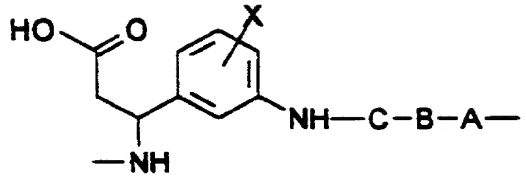
and their salts.

4. Process for the preparation of compounds of the formula I according to Claim 1 and of their salts, characterized in that

(a) a compound of the formula III

H-Z-OH III

in which

Z is 

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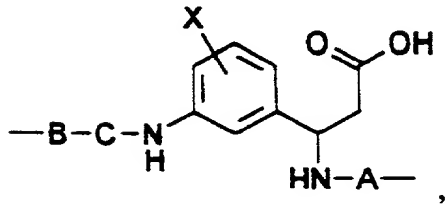

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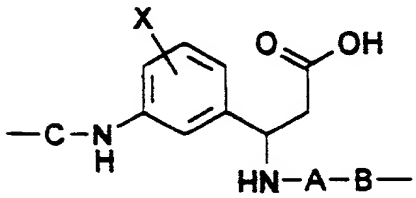
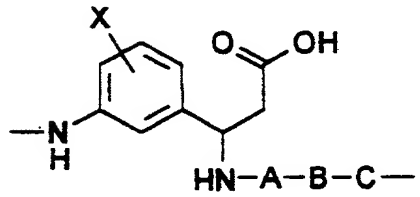


or



and X, A, B and C have the meanings indicated in Claim 1,

or a reactive derivative of a compound of the formula III is treated with a cyclizing agent,

or

b) a compound of the formula I is set free from one of its functional derivatives by treating with a solvolysing or hydrogenolysing agent,

and/or in that a basic or acidic compound of the formula I is converted into one of its salts by treating with an acid or base.

5. Process for the production of pharmaceutical preparations, characterized in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts is brought into a

suitable dose form together with at least one solid, liquid or semi-liquid excipient or auxiliary.

6. Pharmaceutical preparation, characterized in that it contains at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts.

7. Compounds of the formula I according to Claim 1 and their physiologically acceptable salts as integrin inhibitors for the control of diseases of the circulation, thromboses, cardiac infarct, coronary heart diseases, arteriosclerosis, apoplexy, angina pectoris, tumours, osteoporosis, inflammations, infections and restenosis after angioplasty.

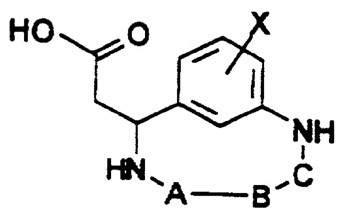
8. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts in pathological processes which are supported or propagated by angiogenesis.

9. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts for the production of a medicament.

10. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts in the control of illnesses.

Abstract

Compounds of the formula I



I

,

in which X, A, B and C have the meanings indicated in Claim 1,

and their salts,

can be used as integrin inhibitors, in particular for the prophylaxis and treatment of diseases of the circulation, in thrombosis, cardiac infarct, coronary heart diseases, arteriosclerosis, in pathological processes which are supported or propagated by angiogenesis and in tumour therapy.

Docket No.
Merck 2075

Declaration and Power of Attorney For Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CYCLOPEPTIDE DERIVATIVES

the specification of which

(check one)

☐ is attached hereto.
☒ was filed on 14 August 1998 as United States Application No. or PCT International Application Number PCT/EP98/05161
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
197 36 772.0 (Number)	Germany (Country)	23 August 1997 (Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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